Pharmacy News

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Special Points of Interest:

- P&T Update-Formulary Additions/ Deletions
- Acute Pyelonephritis in Pregnancy
- Stress Ulcer Prophylaxis in Intensive Care Unit
- ISMP Best Practices for Vincristine (and other vinca alkaloids) Administration
- Fentanyl Use and Safety
- The Future of 3D Drug Printing
- Dantrolene and the Management of Malignant Hyperthermia

P&T Update

Formulary Additions

- **Paclitaxel Protein Bound (Abraxane®)**
  Protein bound paclitaxel is recommended as per the NCCN guidelines for patients at risk for hypersensitivity reactions to paclitaxel. The acquisition cost is $716 per vial versus $36 for the generic paclitaxel.
  Formulary Addition – Approved

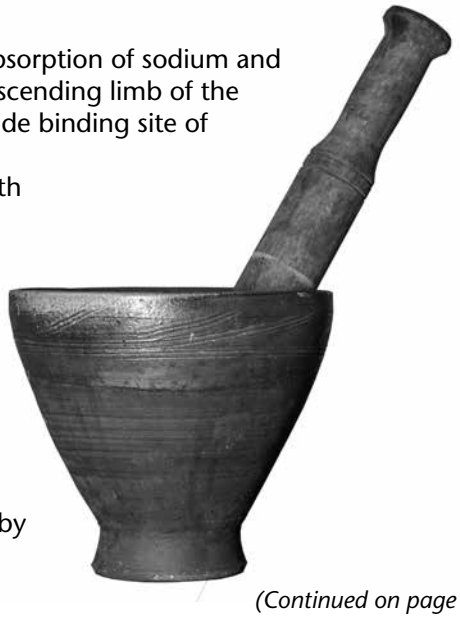
- **Rotavirus RV1 (Rotarix®)**
  CDC recommends oral vaccine to be given by mouth to children at 2 months and 4 months (2-dose series) to prevent rotavirus gastroenteritis
  For patient population in infants ages 6 week to 24 weeks, approval requested and approved for the Ambulatory Care clinic outpatient use
  Formulary Addition – Approved

- **Epoprostenol formulation change**
  Epoprostenol prostacyclin PG12 is a strong vasodilator and potent platelet aggregation inhibitor. It activates adenylate cyclase and results in increased cyclic adenosine monophosphate within the platelets.
  Restrict epoprostenol (Flolan®) generic formulation for cath lab vasodilatory studies only and line extension of epoprostenol (Veletri®) formulation for all other indications - Approved

- **Sodium zirconium cyclosilicate**
  Sodium zirconium cyclosilicate, a nonabsorbed, potassium-binding, inorganic cation exchange crystalline compound that selectively entraps potassium and ammonium in the GI tract, is approved for the treatment of hyperkalemia in adults. Addition of sodium zirconium cyclosilicate to UH Formulary with approval for use initially limited to nephrology and cardiology services

- **Torsemide**
  Torsemide is a loop diuretic. It inhibits reabsorption of sodium and chloride in the luminal membrane of the ascending limb of the loop of Henle by interfering with the chloride binding site of the 1Na+, 1K+, 2Cl– cotransport system.
  Addition of Torsemide to UH Formulary with approval for use

- **Dalbavancin (Dalvance®)**
  Dalbavancin is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by the susceptible isolates of the gram-positive microorganisms. Formulary addition of dalbavancin restricted to H-Blue Observation unit patients and to approval by infectious disease services – Approved



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P&T Updates

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- **Carfilzomib (Kyprolis®)**
  Carfilzomib is a proteasome inhibitor that is indicated as a combination therapy or monotherapy for the treatment of relapsing or refractory multiple myeloma after the patient has received one or more lines of therapy. The first line therapy bortezomib is priced at $895 for 3.5mg vial, carfilzomib 60mg is priced at $1330. Formulary addition of carfilzomib (restricted to the oncology service) – Approved
- **Emtricitabine and Tenofovir alafenamide (DESCOVY®) - Line Extension**
  Descovy® is a combination antiretroviral as a part of HIV treatment regimen. The individual ingredients are already on the formulary. The cost of the combination pill is same as both the ingredients combined. The formulary addition is proposed due to ease of discharging the patient on the combination pill and reduction in medication errors of dispensing separate ingredients individually. Formulary addition of Emtricitabine / Tenofovir alafemide (Descovy®) combination – Approved

Line Extension:

Dtap/IPV (Kinrix®), 0.5 mL IM

- Combination vaccine to ensure vaccine adherence. Formulary Addition – Approved

MMR-V (ProQuad), 0.5 mL

- Combination vaccine to ensure vaccine adherence. Formulary Addition – Approved

Loperamide 1mg/7.5mL

- Removal of 1mg/5mL (no longer manufactured) and addition of 1mg/7.5mL. Formulary Addition – Approved

Formulary Deletions

Selzentry 150 mg tablets

- Request for removal due to low usage; Formulary Deletion – Approved

Phenol 89% bottle

- High risk - request for removal due to low usage; Formulary Deletion – Approved

Cefotaxime Injection

- Medication discontinued by manufacturer; Formulary Deletion – Approved

Loperamide 1mg/5mL

- Medication discontinued by manufacturer; Formulary Deletion – Approved

Hydrocortisone topical formulation mini-class review deletion of certain dosages

- Hydrocortisone is a corticosteroid. Evaluation of topical hydrocortisone on UH Formulary was performed to optimize safety, inventory and cost consideration.

  Currently, UH Formulary includes hydrocortisone creams 0.5%, 1% and 2.5% and ointments 0.5%, 1%, 2.5%
  Proposal was made to delete hydrocortisone 0.5% ointment due to manufacturer discontinuing production
  Formulary deletion of hydrocortisone 0.5% ointment – Approved

  Current UH Formulary hydrocortisone IV are 100mg, 250mg, 500mg and 1000 mg vials.
  Proposal was made to delete hydrocortisone 1000mg vial size due to other vial size available for high dose and current inventory of 1000mg vials size expiring due to no use.
  Formulary deletion of hydrocortisone 1000mg injection – Approved

Desipramine tabs formulation mini-class review deletion of certain dosages

- Currently, UH Formulary includes desipramine 10mg, 25mg, 50mg tablets.
  Proposal was made to delete desipramine 50mg due to alternative strengths are available for higher dose request, and current inventory of 50mg expiring due to no use.
  Formulary deletion of Desipramine 50mg – Approved

Methylprednisolone injectable formulation mini-class review deletion of certain dosages

- Currently, UH Formulary methylprednisolone IV forms are 40mg, 125mg, 500mg, 1000mg, 2000mg vials.
  Proposal was made to delete methylprednisolone 2000mg vial size due to alternative vial size available for high dose (rare to no use). Formulary deletion of methylprednisolone 2000mg injection – Approved

Policies & Procedures/Floorstocks

- Annual Pharmacy Policy Approvals
- UH Department Policy and Procedures
- UH Intravenous Medication Administration Guidelines
- UH Alaris Drug Library
- UH Dangerous Abbreviations - Do not use list
- UH High Risk/High Alert medications
- UH Look-alike/Sound-Alike medications list
- UH Formulary medication list
- Approved

UH Multi-Dose Vial Policy 707-700-105A

- Multi-Dose/Single-Dose Injectable policy updated
  UH protocol has been that all multi-dose medication vials dispensed from the Pharmaceutical Care Division will be labeled with a 'use by' dating auxiliary sticker.
  Added now: Exception: For the procedural areas such as the ORs, the MDVs will NOT be labeled with the "use by" sticker. Multi-dose vials that are brought to the patient bedside and used in these procedural areas such as the OR's should be dedicated to that patient only and discarded after a single use.
  Approved

UH Antibiograms 2018

2018 Antibiogram susceptibility data has been compiled and antibiogram has been updated as per findings – Approved

601-100-0935

707-700-114 Epidural & peripheral nerve catheter Analgesia:

Continuous and Patient Controlled via PCEA pump P&P revision
The PCS education department presented revision of the policy with significant revisions in this version:
Adding nursing involvement in administration and programming of epidurals.
Discussion on possible medication error prevention strategies ensued. Request was made to modify the policy to include
1. Barcode is required and bedside nurse may NOT override the error message.
Provider and pharmacist must be contacted for resolution
2. Catheter tubing confirmation must be performed prior to new bag change.
Catheter must be labeled with "Epidural" or "Peripheral Nerve Catheter"
before proceeding with new med bag change by RN. Provider will be contacted
if catheter label is missing.
Revisions recommended – Approved

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P&T Updates

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707-800-104 Needle Stick Medication Starter Kits for HIV PEP

Update includes:

- Addition of standing prescription order which allows for pharmacy department to dispense one dose of HIV PEP, in the event an exposed individual is not able to seek medical care from ED or Employee Health provider
- Addition of alternative HIV PEP regimen, if unable to utilize preferred HIV PEP regimen
- Extension of duration of supply offered by pharmacy department of HIV PEP to 5 days

Revisions recommended and approved

Pharmacy to dose vancomycin protocol/policy

- Vancomycin is used to treat specific bacterial infections. The efficacy and avoidance of adverse effects (such as nephrotoxicity and ototoxicity) is associated with the maintenance of the serum concentrations within a relatively narrow range. The purpose of this policy is to describe the pharmacokinetic monitoring service provided by the Department of Pharmaceutical Services. – Approved

Adult Hospital Acquired Pneumonia (HAP)/Ventilator Associated Pneumonia (VAP) guideline

- The guidelines encompassing work up, diagnoses, treatment, antibiotic dosing for hospital acquired pneumonia/ventilator associated pneumonia were presented and approved. These guidelines will be available on the policy website and will be incorporated in Epic as feasible. – Approved

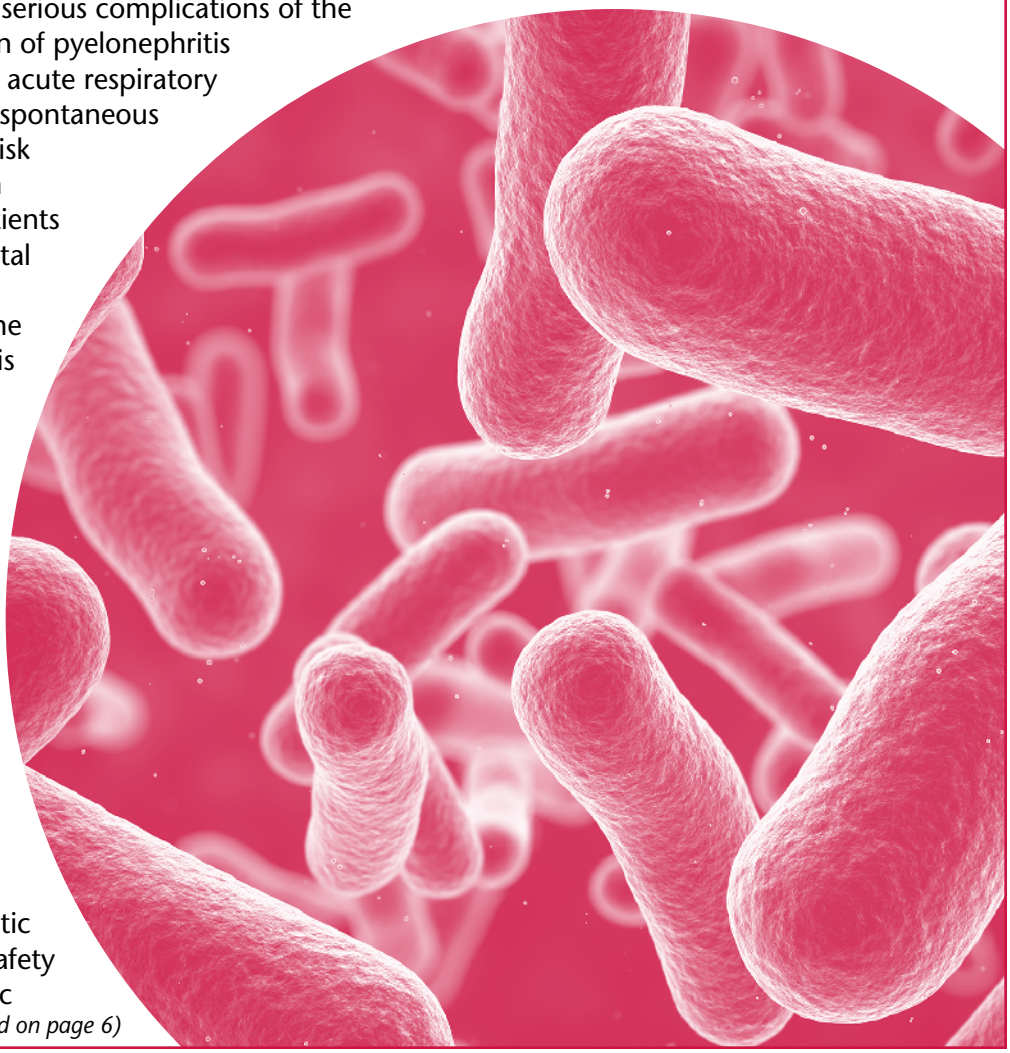
– Policy update approved

Acute Pyelonephritis in Pregnancy

Acute pyelonephritis is a urinary tract infection in the upper urinary tract and kidneys. It is one of the most common medical complications of pregnancy. In the United States it is estimated that 2% of all pregnant women will be hospitalized due to complications related to pyelonephritis. Although urinary tract infections (UTI) are a common occurrence in pregnant patients, a retrospective cohort study conducted by Wing, et al., with a sample size of 543,430 patients, determined the incidence of acute antepartum pyelonephritis to be 0.5%. Over 90% of cases of pyelonephritis in pregnancy are diagnosed in the second and third trimesters. Previous studies have also demonstrated that specific maternal characteristics such as asymptomatic bacteriuria, diabetes, smoking during pregnancy, and late initiation of prenatal care will increase a pregnant patients' risk of acute pyelonephritis. Additionally, about 25% of pregnant women diagnosed with pyelonephritis will have at least one or more recurrent episodes during the same pregnancy.

Escherichia coli causes the majority of acute cases of pyelonephritis in pregnancy. Additional uropathogenic bacteria that cause pyelonephritis in pregnancy includes *Streptococcus, Klebsiella pneumoniae, Staphylococcus, and Enterococcus* species. Pregnant patients with pyelonephritis will typically present with similar UTI symptoms observed in non-pregnant women such as flank pain, nausea, vomiting, and fever. However, some traditional symptoms of UTI such as dysuria are not always present in pregnant women.

It is imperative that pregnant women who develop acute pyelonephritis receive treatment immediately to avoid serious complications of the infection. Common complication of pyelonephritis includes septic shock syndrome, acute respiratory distress syndrome, anemia, and spontaneous preterm birth. Due to the high risk of complications associated with pyelonephritis in pregnancy, patients should be admitted to the hospital for antimicrobial therapy and monitoring for preterm labor. The treatment of acute pyelonephritis includes intravenous antibiotics until the patient improves, is clinically stable and afebrile. For initial empiric therapy of mild to moderate pyelonephritis, cephalosporins are first line for treatment, specifically ceftriaxone or cefepime and often a second antimicrobial effective against Gram negative enteric organisms until the patient is clinically stable. Once the causative uropathogen is identified, empiric therapy can be de-escalated to direct antibiotic therapy. However, due to fetal safety concerns in pregnancy, antibiotic



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Acute Pyelonephritis in Pregnancy

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treatment options are mainly limited to beta lactams, except for in severe cases. Intravenous antibiotics may be converted to oral antibiotic therapy once the patient is stable and afebrile for 48 hours. Then, the pregnant patient can be discharged to complete a 10 to 14 day course of oral antibiotic treatment. When the 10-14 day course of therapy is completed, suppressive antimicrobial therapy is prescribed for the duration of pregnancy.

To prevent acute pyelonephritis in pregnancy, all pregnant patients should be screened for asymptomatic bacteremia with a urine culture for early detection of UTI. According to the clinical practice guidelines for UTI from the Infectious Disease Society of America, the recommendation is that all pregnant women should be screened at least once during weeks 12 to 16 of gestation. Pregnant patients with high risk for infection or recurrent episodes of pyelonephritis such as those with diabetes mellitus, should follow up with repeat urine cultures each trimester to evaluate for the recurrence of bacteriuria.

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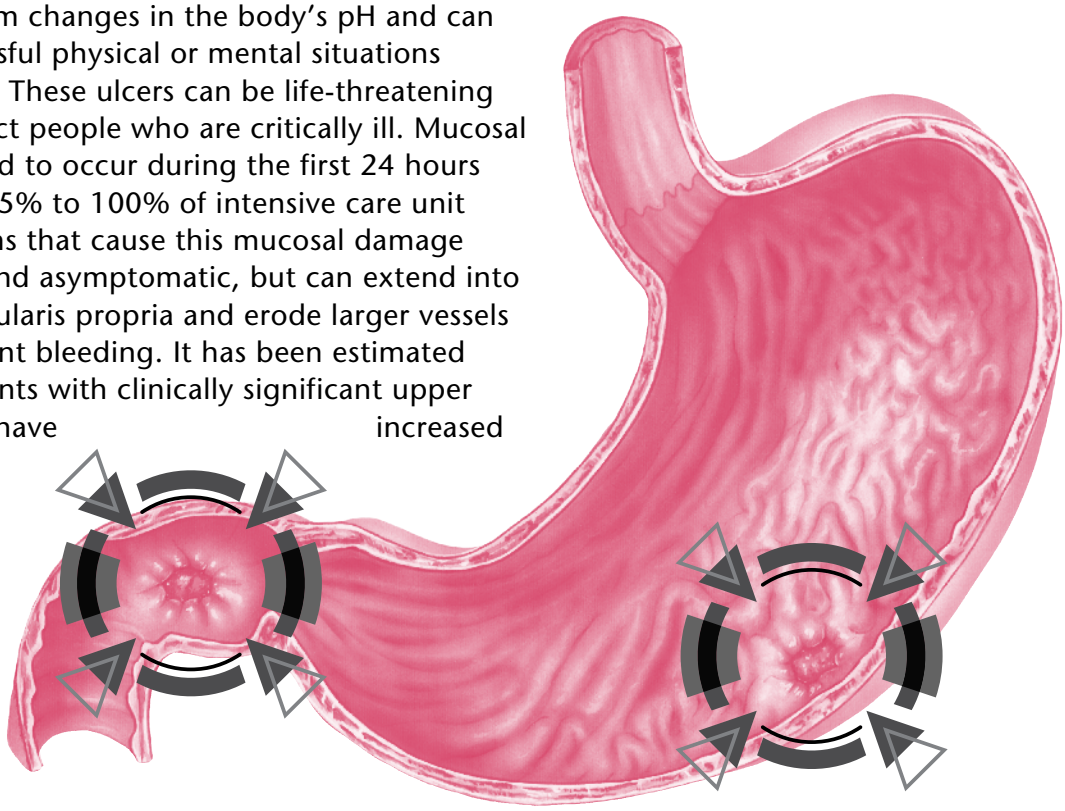
Stress Ulcer Prophylaxis in Intensive Care Unit

Stress ulcers are holes or breaks in the protective lining found in areas of the digestive tract. They can cause sores in the upper gastrointestinal mucosa which can lead to pain, burning sensation, and increase the risk of infection due to low pH. The damage can range from minor irritation to severe bleeding in the GI tract. Stress ulcers are usually caused by *Helicobacter pylori* infection, long-term use of aspirin or NSAIDs, mental stress and spicy foods. Stress ulcers may cause symptoms including stomach pain, bloating, nausea or vomiting while other patients may be asymptomatic.

Several drugs have been used to reduce the incidence of stress ulcers, including sucralfate, histamine-2 receptor blockers (H2RBs) and proton pump inhibitors (PPIs). Sucralfate acts by adhering to epithelial cells forming a protective barrier at the ulcer site, which shields the gastric mucosa from the impact of acid and pepsin. Histamine-2 receptor blockers, such as famotidine and ranitidine, competitively inhibit histamine binding to its G-protein coupled receptor on the membrane of gastric parietal cells, which results in a reduction in acid production.[1] This causes an overall decrease in gastric secretions. Proton Pump Inhibitors, such as pantoprazole, help heal acid damage to the stomach and esophagus, and helps prevent ulcers. It does this by binding to the H+/K+ ATP pump to inhibit gastric acid and basal acid secretion, which prevents acid secretion. Sucralfate can impair the absorption of enteral feeds and co-administered oral medication 2, and has a potential risk of forming a mass of indigestible material that accumulates in the digestive tract, known as bezoar formation, when administering sucralfate to patients who are concurrently receiving enteral liquid nutrients.[3] Due to the fact that sucralfate carries these risks, and H2RBs and PPIs are now widely available, sucralfate is rarely used as a first-line therapy.[4]

Stress ulcers result from changes in the body's pH and can occur in response to stressful physical or mental situations such as being in the ICU. These ulcers can be life-threatening because they tend to affect people who are critically ill. Mucosal damage has been reported to occur during the first 24 hours of hospital admission in 75% to 100% of intensive care unit (ICU) patients.[5] The lesions that cause this mucosal damage are generally superficial and asymptomatic, but can extend into the submucosa and muscularis propria and erode larger vessels causing clinically significant bleeding. It has been estimated that up to half of all patients with clinically significant upper gastrointestinal bleeding have increased mortality in the intensive care unit (ICU) and, in survivors, the length of ICU stay increases by approximately 8 days.[6] Clinically important gastrointestinal bleeding can cause hemodynamic instability and increase the need for red blood cell transfusions as well, therefore, it is intuitive that preventing episodes of clinically significant gastrointestinal bleeding will lead to better patient outcomes.[5] This has led healthcare professionals to be unnecessarily proactive when prescribing proton pump inhibitors for prophylactic use when there is no clear indication for its use.



A recent trial was performed in order to obtain data on the prevalence of gastrointestinal bleeding and the balance between benefits and harms of Stress Ulcer Prophylaxis. In 2018, the stress ulcer prophylaxis in the Intensive Care Unit (SUP-ICU) trial was designed to provide more insight into the pros and cons of taking preventative measures against gastrointestinal stress ulceration. The point of the SUP-ICU trial was to analyze the overall benefits and harms of SUP with proton pump inhibitors in critically ill patients in the ICU. This trial consisted of 3298 patients that were enrolled, 1654 randomly received pantoprazole and 1653 received a placebo. At 90 days the number of patients that had died were 510 (31.1%) of the pantoprazole group and 499 (30.4%) in the placebo group. This trial concluded that among the adult patients in the ICU who were at risk for gastrointestinal bleeding, the number of clinically important events were similar in the pantoprazole group and the placebo group. Using pantoprazole as a prophylaxis did not produce a statistically significant difference in patient mortality or in reducing their chance of gastrointestinal bleeding.[4] This trial resulted in a lack of evidence supporting the use of SUP.

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Stress Ulcer Prophylaxis in Intensive Care Unit

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In the United States, stress ulcer prophylaxis is generally overused in general-care floors as well as the ICU, despite the lack of supporting evidence.[7] Stress ulcer prophylaxis should only be given to patients who are in dire need of it and who have risk factors for bleeding. A national guideline for this medical scenario does not currently exist. The American Society of Health-System Pharmacists Commission on Therapeutics developed a guideline for stress ulcer prophylaxis in 1999 and it has yet to be updated. The outdated guideline recommends stress ulcer prophylaxis in the intensive care unit for patients with any of the following: coagulopathy, prolonged mechanical ventilation (more than 48 hours), GI ulcer or bleeding within the past year, sepsis, a stay longer than 1 week in the intensive care unit, occult GI bleeding for 6 or more days, and steroid therapy with more than 250 mg of hydrocortisone daily.[7] Hemodynamically stable patients admitted to general-care floors should not receive stress ulcer prophylaxis, as it only negligibly decreases the rate of GI bleeding, from 0.33% to 0.22%.[7] The quality of evidence supporting the prophylactic use of proton-pump inhibitors in the ICU is limited. Concerns have been raised about adverse effects associated with this class of drugs, including the risk of Clostridium difficile infection, pneumonia, and myocardial ischemia, which may counterbalance their potential benefits.[4]

In the overall assessment of stress ulcer prophylaxis in today's healthcare system, patients in the ICU may not benefit but instead, could be introduced to increased risks with current treatment options.[4] The SUP-ICU trial showed that there was no evidence to support that the prophylactic administration of proton pump inhibitors are of benefit or harmful to ICU patients. Its lack of proven benefit, additional costs for patients, and risk of adverse effects may be reasons to deter us from using it routinely for hospitalized patients, but it is still used in many instances. Although there is still much controversy that surrounds the use of stress ulcer prophylaxis in ICU patients as well as all hospitalized patients, it is still frequently used today but further clinical trials are required to guide decision-making when it comes to the benefit of stress ulcer prophylaxis.

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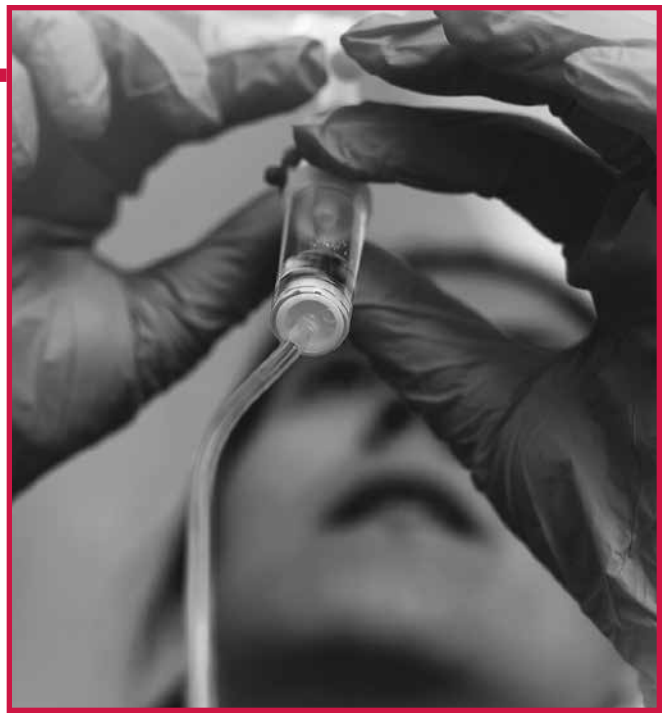
ISMP Best Practices for Vincristine (and other vinca alkaloids) Administration



Vincristine, a major vinca alkaloid, is a common chemotherapeutic agent that has been used for many years. It is indicated for various hematological malignancies and solid tumors for both pediatric and adult populations. Vincristine is used in the treatment of acute lymphoblastic leukemia, non-Hodgkin's lymphoma, myeloma, Wilm's tumor, Ewing's sarcoma and some brain tumors.[1] Vinblastine, vinorelbine and vindesine are other major clinically used vinca alkaloids. Vinca alkaloids are the second-most used class of chemotherapeutics and stay among the original chemotherapies.[2] It must be administered intravenously, otherwise, it can be fatal if given by any other route, especially intrathecally.

The attention to medication errors arose primarily through errors in chemotherapy administration. Despite the long-term use as well as a black boxed warning recommended by the Food and Drug Administration (FDA), incorrect administration of vincristine continues to occur. The Institute for Safe Medication Practices (ISMP) identified the importance of developing a protocol for the safe dispensing of vincristine and other vinca alkaloids as an area for improvement. Many patients receiving intravenous vincristine also receive other medications intrathecally (such as methotrexate, cytarabine and hydrocortisone[3]), as part of their treatment regimen. ISMP has noted that this has led to frequent reports of accidental intrathecal administration of vinca alkaloids. In addition to this, the lack of experience of staff with chemotherapeutics has been identified as a contributing factor to the accidental intrathecal administration. As well as insufficient product labeling, specifically the use of "look alike syringes" during treatment administration, has additionally contributed to these errors.

Upon intrathecal administration, vinca alkaloids can cause potentially fatal neurological defects. They are classified as vesicant drugs and if extravasation occurs, they can cause local tissue injury and necrosis. In addition to this, vincristine is associated with irreversible painful ascending paralysis along with degeneration of myelin and axons. It typically causes erythema, pain and localized swelling within minutes of administration, followed by blistering of the skin over several days which resolves slowly over several weeks. Treatment for the extravasation includes subcutaneous injections of hyaluronidase and warm compresses.[1] Extravasation rarely occurs if the correct administration route is used.

Vincristine, when administered intrathecally, primarily causes peripheral neurotoxicity and is the major dose-limiting side effect associated with its use. It manifests as a combination of sensory and motor neuropathy with symmetrical symptoms which are often reversible after discontinuation of the treatment. The autonomic system and cranial nerves may also experience effects of vincristine neurotoxicity. Vincristine hinders microtubule function resulting in inhibition of axonal transport, thus consequential

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ISMP Best Practices for Vincristine (and other vinca alkaloids) Administration

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degeneration. When administered intravenously, vincristine rarely affects the central nervous system. This is due to the limited perforation into the blood brain barrier.

The effects of intrathecal administration of vincristine are often slow and painful for the patient. Initially, the patient presents with meningitis, and the progression of symptoms occurs from lower limb or back pain to lower limb weakness, urinary retention or frequency, absent reflexes and gradual loss of nerve and muscle function, causing respiratory failure and brain stem death.[1]

In 2001, ISMP recognized and advocated a best practice strategy of vinca alkaloid administration. The strategy involves diluting intravenous vincristine or other vinca alkaloids in a minibag that contains a volume that is too large for intrathecal administration (e.g. 25 mL for pediatric patients and 50 mL for adults), making it mechanically difficult to accidentally administer the drug intrathecally.[3,4] This is an effective prevention strategy that assures a physical barrier to intrathecal administration. Dispensing vinca alkaloids in a minibag, rather than in a syringe, was one of the very first ISMP Targeted Medication Safety Best Practices for Hospitals released in 2014.[5] Other accrediting and professional organizations have also been promoting this safe practice, include, The World Health Organization (WHO), The Joint Commission (TJC) and the American Society of Clinical Oncology (ASCO). According to ISMP's 2018-2019 Targeted Medication Safety Best Practices for Hospitals, no cases of accidental intrathecal administration were reported for vinca alkaloids when dispensed in a minibag.[4]

As of July 2016, University Hospital Pharmacy implemented a policy and procedure for the preparation, dispensing, and labeling of vinca alkaloids (vincristine, vinblastine and vinorelbine). The policy follows the ISMP best practice of vinca alkaloids to be prepared and dispensed in 50 mL D5W IV minibags and labeled with appropriate warning labels to prevent accidental intrathecal injection, stating "Fatal If Given Intrathecally; for IV Use Only." To further assist with the prevention of this potentially fatal error, this class of therapeutics cannot be dispensed together with any intrathecally administered chemotherapy agents.[6] During intravenous administration, central lines are the preferred route of administration due to the vesicant properties of vinca alkaloids. Increased awareness of the potential severity of this medication error, as well as the implementation of ISMP's best practice, can help eliminate improper administration of vincristine and other vinca alkaloid medications, which ensures patient safety.

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Fentanyl Use and Safety

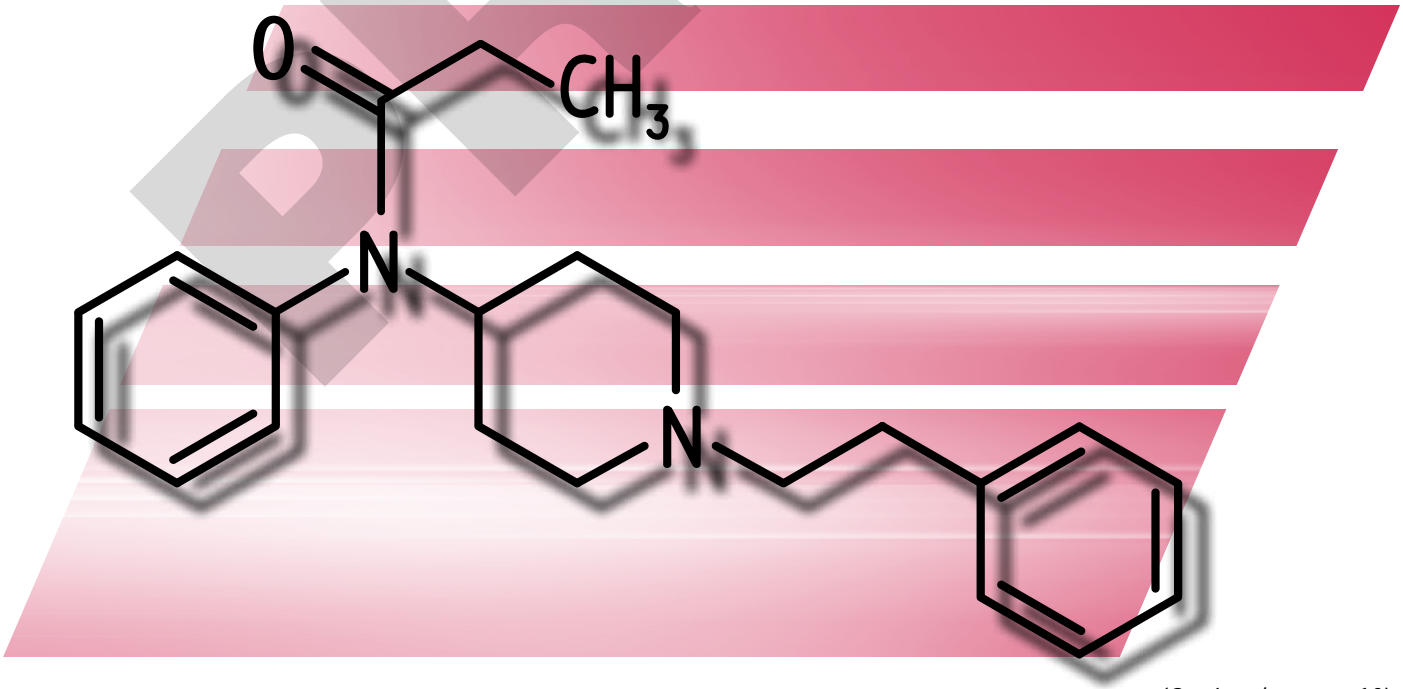
Fentanyl is considered as one of the most dangerous opioids in the world. Each year, thousands of Americans overdose and die from using fentanyl. Many users believe that they are using heroin, unaware that the substance is laced with fentanyl. Most fentanyl in the United States comes from Mexico, Japan, China, and Germany. Due to the lax pharmaceutical regulation, these countries are large distributors of drugs and chemicals that are illegal in other countries. [1]

The United States Drug Enforcement Agent (DEA) issued a nationwide alert on fentanyl as a threat to healthcare and public safety on March 18, 2015. In the last couple of years, the DEA has seen a lot of problems in fentanyl-related seizures. According to the National Forensic Laboratory Information (NFLIS), state and local labs reported 3344 fentanyl submissions in 2014.[2] Fentanyl is commonly laced in heroin causing significant problems across the country, especially as heroin abuse has increased.

Pharmaceutical fentanyl is a synthetic opioid pain reliever, approved for treating severe pain, typically advanced cancer pain. It is 50 to 100 times more potent than morphine. It is prescribed in the form of transdermal patches, lozenges, IV, and nasal formulation and is diverted for misuse and abused in the United States.[3] Fentanyl binds to the body's opioid receptors, increasing dopamine levels in the central nervous system and because of its high potency it's highly addictive.

A recent article on New York Times newsletter has shown that a doctor was charged with killing 25 people over four years by prescribing fatal doses of fentanyl, which is one of the largest murder cases in Ohio's history.[4] The incident happened in the inpatient setting. The doctor had administered doses of 500 to 2000 µg of fentanyl to patients, which caused or hastened the patients' deaths. Also, the amount of fentanyl the doctor was accused of prescribing was much larger than what hospitals allowed to administer to surgical patients.[4]

As stated before, fentanyl is 50 to 100 times more potent than morphine. Street heroin dealers are lacing their products with unknown doses of fentanyl causing an increase in fentanyl-related overdose. Furthermore, the increase in death is not solely from



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Fentanyl Use and Safety
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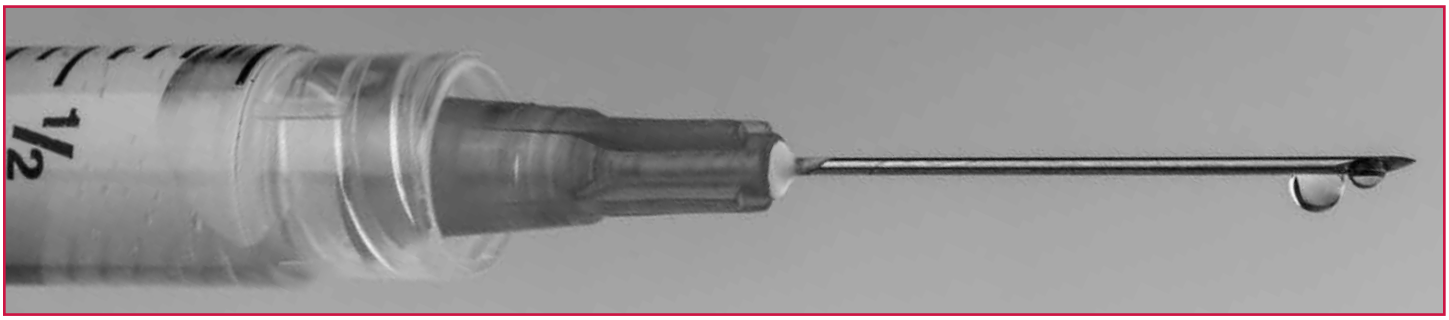
street heroin users. People are also using and abusing prescription fentanyl. Fentanyl transdermal patch misuse and abuse can be caused by applying more than 1 patch to the skin at a time, applying a patch to warm skin or with a heating pad which allows quicker absorption or physically extracting the fentanyl content from the patch. People are becoming more creative with methods of using and abusing these drugs and pinpointing the problem is still a challenge.

because they had temporarily evaded schedule substance laws and remained undetectable on traditional immunoassay test for opioids.[6] In order to combat the issues related to novel fentanyl that was being undetected by law enforcement, a small number of laboratories are becoming equipped with advanced technology devices such as a Tandem mass spectroscopy which has been validated over the concentration range 0.05–100 ng/mL fentanyl in human plasma, based on 0.25 mL sample size.[7]



From a hospital perspective, Pharmacy management teams have developed policies for keeping track of all controlled substances filled at the hospital. For example, at University Hospital, the pharmacy department keeps all controlled substances, schedule II to V, in a safe with access only by designated pharmacist personnel. In order to open the safe, a password and biometric scan are needed. As far as disposal for fentanyl and all the other controlled medications, a double-check system is put in place. The pharmacist disposing of a used/expired fentanyl patch has to sign a paper document and the disposal needs to be witnessed by either another pharmacist or a technician. Laws put in place for hospitals and retail pharmacies regarding controlled medication help minimize drug diversion.

Street diversion of fentanyl became very alarming when more potent forms of fentanyl were being detected in 2015, after a rise in fatalities related to fentanyl overdose. More potent analogs such as carfentanil, acetyl fentanyl, butyryl fentanyl, and furanyl fentanyl were being used in the street heroin.[5] These novel forms of fentanyl became a problem

When a patient is going through an opioid overdose the effects they experience are usually respiratory or central nervous system depression. In an opioid overdose case, an opioid antagonist needs to be administered to reverse the effects caused by the overdose. Full opioid antagonist such as naloxone competes at all the opioid receptor subtypes to reverse most of the adverse effects caused by an opioid agonist. A breakthrough in combating the opioid epidemic was the approval of Narcan (the nasal formulation of naloxone) back in November 2015 by the FDA. According to an article on the FDA website "This easy-to-use intranasal formulation will no doubt save many lives," said Nora Volkow, M.D., director, National Institute on Drug Abuse at the National Institutes of Health. "While prevention is the ultimate goal, the drug's successful development illustrates how public/private scientific partnerships can play an important role in responding to a national crisis right now."[8] Narcan is easy to use and can be used by a layperson and emergency medical services alike.

In response to the alarming crisis of fentanyl and all other opioid agonists related death the State of

New Jersey was recently part of the free Naloxone day on June 18, 2019. Here at University Hospital of New Jersey, the emergency department was gave away Naloxone kits to patients who had an overdose free of charge. Aside from that date University hospital should consider implementing their own special event where they give naloxone free of charge to patients/families in need. In closing statement; if you or know someone with an addiction problem please feel free to call 2-1-1 for help it's never too late.

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The Future of 3D Drug Printing

Three dimensional (3D) printing of drugs is a milestone in the pharmaceutical industry that involves customizing of medication so that they suit individual patients (Ventola, 2018). The size, appearance, and rate of delivery are all customized, in a way that makes the drugs safer and more efficient. For instance, the FDA has already approved Spritam, which uses 3DP technology in the creation of a more porous pill that can be swallowed quickly. The 3D printing of drugs engages three methods that are inclusive of selective laser sintering, stereolithography, inkjet printing and binder deposition. The method of printing 3D drugs is a fusion of deposition modeling and extrusion based printing.

Some of the traditional medicinal drugs such as penicillin are still very important in healthcare provision and would pose competition to the 3D printed drugs. Secondary sources suggest that penicillin pointed the way towards the pharmacological management of microbial diseases. 75% of current human population owes its existence to the advent of penicillin and its derivatives. Some pharmaceutical companies such as AstraZeneca and Gilead Sciences are likely to pose competition to the 3D drug printing because such companies are already best known in the production of classes of drugs like antivirals. Such pharmaceutical companies have solid commercial portfolio rich in life saving drugs in respiratory and cardiovascular therapies.

The 3D printing of drugs also faces competition from other generic and chemically derived drugs whose mode of function is the same as the current technologies. Innovative chemically-derived drugs are derived from clinical trials and extensive research and development in both animals and human test subjects (Hsiao,

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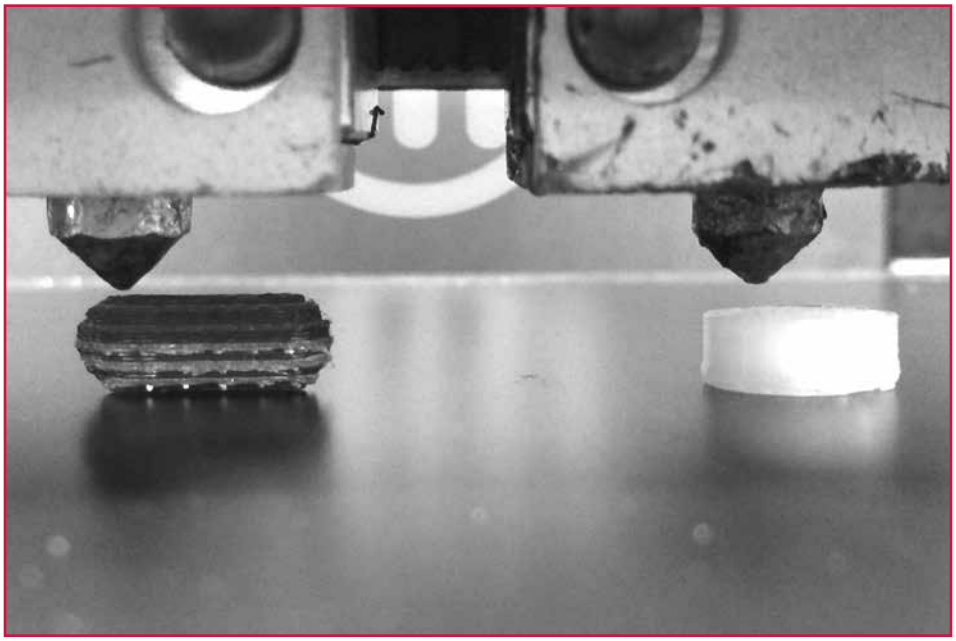
Lorber, Reitsamer & Khinast, 2017). The producers of generic and innovative drugs researched and embraced technology that make it easy for them to meet the FDA bio-equivalent standards and approval, therefore, posing as potential competitors to the producers of 3D printed drugs. (3D drug production prototype)



Other potential competition in this regard involves the batch manufacturing in the production of drugs. The batch process consists of the addition of ingredients in successive but disconnected steps (Ventola, 2018). A team of researchers recently found out that the process could even be made faster through the integration of several new chemical processes and specially made equipment. This will pose as competition to the already tested 3D printing of drugs, in addition to the conventional drug production by pharmaceutical industries.

The evolvement of 3D printing of drugs is viewed as a revolutionary force in the realm of pharmaceutics. Through complex 3D printed geometrics and architecture therein, the pharmaceutical industries can now control the release characteristics of drugs. As a result, there is a reality of engineering of precise and unique doses, fabricated through 3D printing. Also, the doses produced through the 3D printing of drugs are in accordance with individual prescriptions. On-demand printing of drugs has also been applicable in the manufacture of drugs with limited shelf-life. As a result, the 3D printing has offered alternatives to what used to be traditional compounding pharmacies (Lepowsky & Tasoglu, 2018).

The 3D printed drugs are recognized as personalized medicine. The problem the technology solves is about the ineffectiveness and consumption difficult that other conventional drugs come with (Dodziuk, 2016). With the new technology, the 3D printed drugs are easy to consume and more efficient in the regular medication schedule.

Through a 3D prototyping of different layers of fabrication, the 3D printing of drugs has reduced the drug production time which concurrently achieves unparalleled flexibility. Desired dosage forms can be formulated from drug materials promptly through computer aided design models, hence solving the problem of delay in the production process.

The 3D drug printing technology does not replace but only enhances the current process. The first item that 3D printing of drugs enhances is the productivity. Within several hours, complete products can be produced, making the current technology faster than traditional drug processing method. With traditional methods, the process of making drugs requires longer production time and multiple stages. Other capabilities that have been added to the traditional methods include accuracy, resolution, and reliability.

The 3D printing has also come with democratization and collaboration that were not

there in the traditional methods. Different materials are now becoming available for use in the production of 3D printed drugs, most of which are decreasing in cost. Therefore, more people in the medical fields are using more than just 3D printers in designing and production of novel products for commercial and personal use.

Some of the benefits associated with the 3D printing of drug technology are in line with making drugs cheaper, more accessible and personalized (Lepowsky & Tasoglu, 2018). Combination therapy can also include the 3D printed drugs and other conventional drugs. In the same way, 3D printed drugs can act as a second option for people who struggle with their current experience with medications, solving such problems as swallowing large pills.

The 3D printing of drugs also enhances the current process through a realization of manufacture of very porous pills. The ingestion of such drugs is also believed to be highly enhanced, and, therefore, easily ingested due to the small size of the drug as well as the combination of various pharmacologic agents. Consequently, it will be right to say that the 3D printing of drugs has improved the previous processes.

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Dantrolene and the Management of Malignant Hyperthermia

Malignant hyperthermia (MH) is a rare inherited disorder of skeletal muscle triggered in susceptible individuals by commonly used inhaled general anesthetics and the paralyzing agent succinylcholine, resulting in hypermetabolism, skeletal muscle damage, hyperthermia and death if untreated. Patients at risk for MH have mutations in their muscular dihydropyridine or ryanodine receptors, which leads to unregulated passage of calcium into the intracellular space when exposed to triggering agents. This accumulation of calcium causes sustained muscle contraction.

When exposed to triggering agents, MH can occur within minutes. Signs and symptoms of MH include hypercarbia, muscle stiffness, hyperthermia, metabolic acidosis, cardiac arrhythmias, and hemodynamic instability. Due to similar symptoms, MH can be confused with other emergencies such as serotonin syndrome or neuroleptic malignant syndrome. However, recent administration of a general anesthetic prior to development of symptoms warrants immediate treatment of MH.

The primary drug used to treat MH is dantrolene. Dantrolene is a direct skeletal muscle relaxant that acts by interfering with release of calcium ion

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from the sarcoplasmic reticulum. The recommended dose of dantrolene for acute management of MH is 2.5 mg/kg IV bolus through a large bore IV. The bolus dose can be repeated as needed every 5 to 15 minutes, until symptoms subside. Large cumulative doses of greater than 10 mg/kg may be required for patients with persistent symptoms. In addition to dantrolene, supportive measures, such as active cooling, should be performed to manage symptoms.

Procurement of dantrolene involves multiple vials and steps, so it is crucial to stay familiarized with the location and dilution process for when MH occurs. The Malignant Hyperthermia Association of the United States (MHAUS) recommends that dantrolene be stored where it can be accessed quickly in areas where triggering agents are administered frequently, such as the Operating Room or Emergency Department. The locations for dantrolene at University Hospital and procedures for managing an MH crisis can be found on MCN.

Although the incidence of MH is very low, it is important to be able to recognize it when it does occur. Prompt recognition and treatment with dantrolene ultimately decreases the risk of death. If additional assistance is needed in case of an MH crisis, healthcare providers are encouraged to call the 24-hour MH hotline run by MHAUS at (800)-644-9737.

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